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2013

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Holly A. Shill

Barrow Neurological Institute, holly.shill@dignityhealth.org

Terry D. Fife

Barrow Neurological Institute, tfife@email.arizona.edu

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Recommended Citation

Shill, Holly A. and Fife, Terry D., "Causes of Imbalance and Abnormal Gait That May Be Misdiagnosed" (2013). *Neurology*. 66.

<https://scholar.barrowneuro.org/neurology/66>

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Causes of Imbalance and Abnormal Gait That May Be Misdiagnosed

Holly A. Shill, MD¹ Terry D. Fife, MD²

¹Christopher Center for Parkinson Research, Banner Sun Health Research Institute, Sun City, Arizona

²Department of Neurology, Barrow Neurological Institute, University of Arizona College of Medicine, Phoenix, Arizona

Address for correspondence Holly A. Shill, MD, 10515 W., Santa Fe Dr., Sun City, AZ 85351 (e-mail: Holly.shill@bannerhealth.com).

Semin Neurol 2013;33:270–275.

Abstract

Keywords

- Segawa's disease
- gait difficulty
- imbalance
- ataxia
- gluten ataxia
- bilateral vestibular loss
- essential tremor

Disorders of gait and balance are common in medicine and often lead to referral for neurologic evaluation. Because the maintenance of balance and normal gait are mediated by complex neurologic pathways as well as musculoskeletal, metabolic, and behavioral considerations, the list of possible contributing causes is very large. Much of the time, the history and neurologic examination reveal the underlying cause or causes. There are instances, however, when there are limited neurologic findings, as well as no structural abnormalities on brain or spine magnetic resonance imaging studies to explain the imbalance or gait difficulty. In this article, selected disorders that may be overlooked in the neurologic examination and imaging studies are reviewed. Possible causes of imbalance include occult drug-induced ataxia, autoimmune ataxia, ataxia associated with tremor, bilateral vestibular hypofunction, and spastic or dystonic gait disorders with normal imaging.

Disorders of gait and balance are among the more common clinical complaints, particularly among older patients.¹ Because so many medical and neurologic conditions can influence balance and ambulation, a thorough evaluation is often necessary. Thus, a neurologic examination, brain imaging, and sometimes electrophysiologic studies are done to identify contributing causes and to assess and to try to reduce the risk of falling.²

In many instances, the history and examination reveal the likely causes. In other cases, brain magnetic resonance imaging (MRI), spine MRI studies, electromyography, and nerve conduction studies are necessary to confirm the likely mechanism. In some instances, even after a thorough neurologic history and examination and extensive imaging studies the cause of the imbalance or gait disturbance remains unclear. Commonly, a multitude of contributing factors separately contribute to disturbance of gait or balance. Other times, no convincing cause can be determined. ► **Table 1** lists disorders that may present with gait ataxia.

This review will focus on selected causes of imbalance or disturbed gait that may be overlooked even in the face of a

thorough neurologic, imaging and electrophysiological evaluation.

Drug-Induced Gait Ataxia

Ataxia is a common manifestation of many drugs and toxins. For instance, most of the antiepileptic agents have ataxia as a relatively common acute adverse event; phenytoin, phenobarbital, and carbamazepine, in particular, may also have a dose-related adverse effect on balance.³

However, there are several agents that warrant discussion as it might not be obvious that the drug is the causative agent primarily because the onset of gait disturbance may be quite delayed, mimicking a degenerative condition.

Lithium Ataxia

Lithium is an agent primarily used for mood stabilization in bipolar illness. Because of the narrow therapeutic window and need for blood monitoring, it is less commonly used in favor of agents such as quetiapine and lamotrigine. However, many patients are still chronically receiving treatment with

Table 1 Disorders that may present with gait ataxia

Toxins/drugs	Infectious	Metabolic	Basal ganglia	Genetic	Autoimmune
Ethanol	Creutzfeldt-Jakob disease	B12	Early Parkinson's disease	Dominant	Generalized anxiety disorder
Phenytoin	JC virus	Wernicke's encephalopathy	Progressive supranuclear palsy	Recessive	Gluten sensitivity
Lithium	Viral		Multiple system atrophy	Mitochondrial	Hypothyroidism
Amiodarone	Postviral	Other	Corticobasal degeneration	X-linked	Hashimoto's encephalopathy
Isoniazid	Whipple's	Segawa's disease		DNA repair	Paraneoplastic
Metronidazole		Spinal arteriovenous malformation			Miller-Fisher syndrome
Platens	Structural				
Cyclosporine	Tumor				
Valproic acid	Demyelinating				
	Vascular				
	Abscess				
	Sarcoid				
	Hydrocephalus				

lithium. Ataxia may develop insidiously after many years on the drug, even though the patient has normal serum levels and lithium tremor may be absent.^{4,5} Subtle cerebellar signs may be variably present, but might not be immediately recognized. Recognition that lithium may be causing the imbalance is important as this condition is mostly reversible if the drug is stopped early. However, it may be irreversible if there are complicating factors such as acute infection with hyperthermia or concomitant use of neuroleptics.⁶

Valproate-Related Ataxia

Valproic acid is another drug well known to produce tremor shortly after starting the drug.⁷ Reversible parkinsonism and cognitive impairment are also recognized with a delayed onset similar to what is seen with lithium.⁸ Reversible cerebellar dysfunction that begins with gait ataxia has been seen with this drug⁹ anyone with a suspected neurodegenerative disease that begins while on chronic valproate should be considered for discontinuation even if (1) the individual has been taking the drug for years, and (2) the drug levels are in the normal range. The full improvement may take several months (similar to tardive dyskinesia); consequently, the slow recovery after cessation of the valproic acid is still consistent with a cause and effect relationship and should not be discounted until ~6 months after discontinuation of the drug.

Amiodarone-Related Imbalance

Amiodarone is a drug used in the treatment of life-threatening ventricular arrhythmias. In addition to pulmonary and thyroid toxicity, neurologic side effects can be seen.^{10,11} Tremor, parkinsonism, and peripheral neuropathy are the most commonly reported. Severe, progressive gait ataxia has been reported as well and appears to be reversible upon stopping the drug.¹²⁻¹⁴

Bilateral Vestibular Hypofunction

Bilateral peripheral vestibular loss is an uncommonly recognized cause of imbalance that may be acquired either from degeneration, sequential bilateral vestibular neuritis, or from ototoxicity, usually related to gentamicin. It can lead to unsteadiness with few obvious neurologic signs. It can lead to particularly difficult problems with imbalance in certain subsets of patients with pre-existing somatosensory or visual impairment. As an example, a diabetic patient with severe longstanding polyneuropathy from diabetes may receive gentamicin during a hospitalization for infection; after recovery from the acute illness, the patient seems unable to regain the ability to maintain balance or walk safely due to vestibular loss. The combination of vestibular and proprioceptive sensory loss renders the patient severely off balance despite normal motor power. Patients may report particular difficulty in darkness (when deprived of vision) and sometimes oscillopsia (perception of "bouncy" vision during locomotion). Examination will show an abnormal head impulse test in both directions and severely reduced caloric vestibular responses.¹⁵ Bilateral vestibular loss has a reasonably good long-term prognosis for functional recovery when it is an isolated deficit.¹⁶

Tremor and Ataxia

Essential Tremor and Ataxia

Essential tremor is a very common neurologic condition occurring in ~5% of those over age 40.¹⁷⁻¹⁹ The incidence increases with age and may be as high as 20% in those over the age of 80. Gait and balance issues are common in advanced age; it is often common to simply attribute instability to aging, in the absence of any other clearly identified cause.

However, it is clear from several studies that some patients with essential tremor are at a higher risk for developing difficulty walking; therefore, tremor and ataxia may correlate in some individuals. A study of 36 essential tremor patients and 40 age-matched controls demonstrated 50% of patients with essential tremor had abnormalities of tandem gait compared with 28% of controls. The abnormality was greater in those older than 70 ($N = 22$) and those with essential tremor longer than 5 years ($N = 28$).²⁰ It was suggested that this finding was related to the reports of cerebellar dysfunction seen on blood flow imaging studies,²¹ which has been confirmed in other studies subsequently.^{22,23} Another study followed up on the findings by Singer et al to show a similar pattern of gait disturbance. This study of 25 patients with essential tremor were analyzed with kinematic analysis and compared with controls and those with known cerebellar diseases.²⁴ Findings in cases of essential tremor were similar to those with cerebellar diseases, and different from controls, with a widening of gait in normal walking, changes in the heel strike pattern, and distinct problems with the balance of tandem gait. More abnormalities were seen in those with intention tremor over postural tremor; duration of disease did not seem to be a factor.

Follow-up studies have further examined the gait of essential tremor. It seems as though it may be alcohol responsive with improvement of tandem gait with modest amount of ethanol compared with worsening of gait in controls.²⁵ Similarly, functional neurostimulation of the motor nucleus of the thalamus may improve gait in essential tremor, independent of tremor control.²⁶ These last two studies taken together suggest that the gait abnormality of essential tremor may be a functional disturbance rather than pathologically mediated.

Orthostatic Tremor

Orthostatic tremor does not produce a gait disturbance per se, but rather a disturbance of stance.²⁷ It is seen in older individuals (mean age mid-50s) and is characterized clinically by repeated, irregular buckling of the legs and leg cramps while the patient is maintaining stance.²⁸ There is often latency of onset of buckling of up to 3 minutes. Underlying the buckling is a high-frequency tremor that may be picked up by electromyography, but is usually not observed because of its fine, rapid nature. Because of the frequency range of the tremor (13–18 Hz), the tremor might also be audible with a stethoscope as a low thumping sound.²⁹ Orthostatic tremor can be seen with parkinsonism in ~25% of cases and is associated with essential tremor in some studies³⁰; however, it is most commonly idiopathic.²⁸ It often responds to treatment with clonazepam or gabapentin, so this condition should not be overlooked.³¹

Fragile X-Associated Tremor/Ataxia Syndrome

Fragile X-associated tremor/ataxia syndrome is a late-onset neurodegenerative disorder presenting in men over the age of 50. It occurs in carriers of a premutation range expansion of the CGG-repeat causative of fragile X mental retardation (X-

linked recessive disorder). The disorder typically begins with action tremor followed by gait ataxia within 2 to 3 years. With progression, there may be parkinsonism, dementia, peripheral neuropathy, and autonomic impairment. Magnetic resonance imaging may only show hyperintensity in the middle cerebellar peduncles. Family history of mental retardation in cousins and grandchildren may be present. The carrier frequency of the premutation in the general population is estimated at 1 in 213 for females and 1 in 813 in males.³² Penetrance is age related with 75% of male carriers manifesting symptoms once over 80 years old.³³ This makes this condition similar in prevalence to multiple system atrophy and amyotrophic lateral sclerosis. It seems to be rare in pure presentations of various movement disorders. For instance, the FMR1 premutation is rare to absent in classic essential tremor and Parkinson's disease.^{34,35} However, screening a cerebellar type of multiple system atrophy and late-onset cerebellar ataxia in men may produce a positive rate of 5%.³⁶ Based on these types of studies, a review has suggested that FMR1 premutation screening be performed in cerebellar ataxia of unknown cause in individuals over the age of 50.³⁷

Other Genetic Ataxias in Late Adulthood

Episodic ataxia type 2 (EA-2) is a genetic disorder that leads to episodes of dizziness and ataxia. In some patients, there are no neurologic abnormalities evident between attacks, whereas in others, there is a slowly progressive ataxia that develops between the attacks characterized by downbeat and/or gaze-evoked nystagmus and gait ataxia. EA-2 is associated with more than 20 distinct CACNA1A mutations and the list is growing.³⁸ SCA 6 is allelic with episodic ataxia 2 (EA-2) and there appears to be some phenotypic overlap between the two conditions with some patients initially having an intermittent ataxia before going on to develop a more chronic, progressive course.^{39–41} It presents as a relatively pure cerebellar ataxia with gait often affected first. Noncerebellar signs occur less frequently and include decreased vibration/proprioception and impaired upgaze. The frequency of SCA6 is more common in Japanese and German ataxia families.⁴² Because of the older age of onset (mid-50s) and relatively normal life span, family history may not be immediately obvious; up to 30% of SCA6 may be mislabeled as sporadic ataxia. The episodic ataxia may be responsive to acetazolamide and perhaps in some instances 4-aminopyridine.⁴³

The autosomal recessive adult cerebellar ataxias include late-onset Friedrich's ataxia and α -tocopherol (vitamin E) deficiency. Both produce an indistinguishable clinical phenotype characterized ataxia with signs of posterior column involvement, areflexia, and extensor plantar responses.⁴⁴

Autoimmune-Mediated Ataxia

Gluten Ataxia

It has been recognized for some time that celiac disease may be associated with neurologic manifestations including sensory neuropathy and ataxia.⁴⁵ However, in the last 10 to 15 years, it has become clear that these neurologic disorders

can present even in the absence of malabsorption or other gastrointestinal symptoms.⁴⁶ These patients present with severe gait ataxia without other cerebellar findings. Some have a sensory neuropathy or ganglionopathy.⁴⁷ Gluten sensitivity may be detected by the presence of antigliadin antibodies (IgA/IgG) and tissues transglutaminase. Intestinal biopsy may show lymphocytic infiltration and changes typical of celiac disease even without classic gastrointestinal symptoms in ~75%.⁴⁸ Approximately 30% of sporadic ataxia may show antibodies to gluten compared with 10% of controls.^{49–51}

What is not entirely clear is whether the antibodies are causative of ataxia or merely epiphenomena. However, recent studies have suggested that the gluten sensitivity may be pathogenic as there are now several reports of the neurologic condition stabilizing or even improving with strict adherence to a gluten-free diet.^{47,52,53} Additionally, treatment with intravenous immunoglobulin may be of benefit.⁵⁴ Based on these studies, it is recommended that patients with sporadic ataxia and/or progressive sensory ganglionopathy be screened for antigliadin antibodies. Those positive should be considered for dietary management. Follow-up with periodic antibody testing is crucial to ensure dietary compliance.

Hashimoto's Encephalopathy (Autoimmune Thyroiditis)

Patients with Hashimoto's encephalopathy present with a variety of neurologic and psychiatric symptoms including tremor, confusion, seizures, and psychiatric symptoms. Ataxia has also been reported as a primary manifestation of autoimmune thyroiditis.^{55,56} Patients present with a subacute or chronic cerebellar process. There may be a history of other organ-specific autoimmune disorders. Imaging may show cerebellar atrophy in more chronic patients. Laboratory testing shows elevated levels of antithyroglobulin and antithyroid peroxidase antibodies. Prednisone may result in rapid improvement in some,⁵⁶ but not all⁵⁵ patients. Some patients may respond to intravenous immunoglobulin.⁵⁵

Paraneoplastic Disorders

The acute to subacute onset of gait ataxia with normal imaging should prompt consideration of a paraneoplastic disorder. Anti-Yo (gynecological cancers and Hodgkin's lymphoma) and anti-Ri (neuroblastoma) can both produce a cerebellar disorder.^{57,58} Anti-Hu (small-cell lung cancer) can produce a cerebellar ataxia syndrome, usually with cerebellar examination abnormalities, including ataxic gait, limb clumsiness, impaired pursuit eye movement tracking, and gaze-evoked nystagmus. Anti-Hu antibodies may also result in other paraneoplastic neurologic syndromes including sensory neuronopathy (Denny-Brown syndrome) and limbic encephalitis.⁵⁹ Overlap of the various clinical syndromes can be seen such that antibody screening is best performed more globally unless the underlying cancer is already known. Onset of the neurologic disorder can precede the detection of the underlying cancer by months to years in approximately two-thirds whereas the rest are seen when the cancer has been treated and may be no longer detectable.

Periodic cancer screening should be performed in anyone with positive antibodies where the cancer was not detectable on initial evaluation.

Gait Abnormality with Hyperreflexia and Normal Imaging

Adult-Onset Dopa-Responsive Dystonia (Segawa's Disease)

Dopa-responsive dystonia is an autosomal dominant dystonia that usually begins in the first decade of life as the child begins to walk.^{60,61} Infrequently, however, the onset of symptoms can occur much later in life,⁶² resulting in a very long interval between onset of symptoms and an actual diagnosis.⁶³ The symptoms consist of gait disturbance categorized by toe walking and sometimes torsion dystonia of the lower limbs later involving the upper extremities. Over decades, patients may develop postural tremor and mild parkinsonian features (except rest tremor). A key feature in children is the clinical symptoms have marked diurnal variation with exacerbation of symptoms in the evening and often complete resolution by morning after sleep. Another feature is that of hyperreflexia with flexor plantar reflexes, slow movements, stiffness, and balance difficulty.

The most common genetic abnormality seen in dopa-responsive dystonia is guanosine triphosphate cyclohydrolase I deficiency. With identification of a causative gene, other phenotypes have been identified including a later age of onset, a more focal task specific dystonia or even simple parkinsonism.⁶⁴

Onset after the age of 18 seems to be rare, perhaps less than 10%, but the disorder can be seen as late as the sixth decade. In addition, the gene has variable penetrance such that a family history might be absent. Treatment is with carbidopa/levodopa and the response is typically quite dramatic. Patients remain medication responsive and usually do not develop motor fluctuations or dyskinesias as with typical Parkinson's disease. Often, by the fourth decade, levodopa can be weaned successfully. Other conditions may mimic dopa-responsive dystonia including hereditary spastic paraparesis, Wilson's disease, cerebral palsy, and Parkin mutation (young-onset recessive Parkinson's disease). Because of the unique sensitivity of this disorder to treatment, a trial of levodopa should be considered in a patient of any age presenting with a gait disturbance characterized by lower extremity stiffness and hyperreflexia without causative central nervous system abnormality on imaging. The peculiar appearance of the gait may sometimes lead to the erroneous diagnosis of a conversion disorder or psychiatric gait disorder.

Spinal Dural Arteriovenous Fistula

These lesions represent the majority of spinal vascular malformations. The most common clinical presentation is that of an often fluctuating, progressive myelopathy in middle-aged men. Clinical signs are due to venous congestion causing cord compromise. Findings on MRI may be missed or absent on traditional sequences; magnetic resonance angiography may be helpful, but neither replaces the need for arteriography.⁶⁵

Findings on traditional MRI may only show subtle T2 hyperintensity (80%); flow voids can usually be seen, but require especially careful inspection (89%).⁶⁶ The presence of either of these two features has a sensitivity of 100% in predicting an arteriovenous fistula at arteriography or surgery. The identification of these lesions is crucial as successful treatment can stabilize or improve disability.⁶⁷

Nutrient and Mineral Malabsorption Syndromes

It should be remembered that in patients with spasticity and gait difficulty with a prior history of bariatric surgery or who may be prone to short bowel malabsorption, should be assessed for copper deficiency-related myelopathy or vitamin E or B12 deficiency states.⁶⁸

Conclusion

There are many causes of gait ataxia. Many of these can be identified based on the presence of additional neurologic findings as well as findings on imaging and neurophysiological studies. When no cause is immediately evident, the etiology may declare itself over time and close follow-up is warranted.

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